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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
TURNER, SHARON L	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 11/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary	Application No.	Applicant(s)	
	09/806,842	MASLIAH ET AL.	
	Examiner	Art Unit	
	Sharon L. Turner	1647	

-- The MAILING DATE of this communication app ars on the cover sh et with th correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 September 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-8 and 11-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-8 and 11-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *4-8 and 11-13* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 April 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7-12-01* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The amendment filed 9-2-03 has been entered into the record and has been fully considered. Claims 1-3, and 9-10 are cancelled. Claims 11-13 are newly presented. Claims 4-8, and 11-3 are pending.

2. The amendment of 9-2-03 is objected to because of the following informalities: The marked up copy of the claim amendments as submitted 9-2-03 do not accurately reflect the changes made. Applicant's response should include a new marked-up copy that accurately reflects the claim amendments.

Specification and Sequence Compliance

3. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth herein. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be examined under 35 U.S.C. §§ 131 and 132.

In particular, Figure 3 denotes amino acid sequences but fails to identify the sequences by appropriate SEQ ID NO: as required. If the sequences are already represented by an appropriate SEQ ID NO:, then applicant need only amend the specification to refer to the sequences within the figure by appropriate residues and/or SEQ ID NO:. Otherwise, applicant is required to create a SEQ ID NO as appropriate. Such would necessitate a substitute computer readable form (CRF) copy of the "Sequence Listing" which includes all of the sequences recited in the claims and specification of the instant application and encompassed by these rules, a substitute paper copy of that "Sequence Listing", an amendment directing the entry of that paper copy into the specification, and a statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. §§ 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d). The instant specification and/or claims will also need to be amended so that they comply with 37 C.F.R. § 1.821(d) which requires a reference to a particular sequence identifier (SEQ ID NO:) be made in the specification and claims wherever a reference is made to that sequence. For rules interpretation Applicant may call (703) 308-1123. See M.P.E.P. 2422.04.

4. The disclosure is objected to because of the following informalities: The specification is objected to as failing to comply with the sequence rules which requires reference to all amino acid sequences greater than 4 amino acids in length by SEQ ID NO:.

Appropriate correction is required.

Drawings

5. The drawing of Figure 3 is objected to because the figure lacks sequence compliance. A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance. Appropriate drawing correction may be effected by appropriate amendment to the specification and compliance with the sequence rules as noted above.

Election/Restriction

6. Applicant's election of Group II, claims 4-8 in the Paper of 9-2-03 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Newly submitted claims 11-13 are directed to the invention of Group II and are under examination.

Claim Objections

7. Claim 7 is objected to because of the following informalities: The claim lacks an appropriate article between "protein" and "modulates". Appropriate correction is required.

Claim R j ctions - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 4-8 and 11-13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection. Applicants new claims recite "A method for screening for treatments for neurodegenerative disease comprising inducing aggregation of amyloidogenic proteins; exposing amyloidogenic proteins to a treatment; measuring aggregation of NACP/α-synuclein and measuring aggregation of NACP/α-synuclein to test for a decrease in aggregation, wherein the decrease is indicative of an effective treatment." Applicant's have not provided support for the claim amendments. Further, new claims 11-13, recite "wherein the aggregation is induced by oxidative stress," "wherein the treatment comprises an agent to promote the expression of anti-amyloidogenic proteins," and "wherein the anti-amyloidogenic protein is β-synuclein." However, applicant's have not provided supoort for the new claim recitations as recited and the Examiner fails to find apparent support. Thus, the newly recited methods constitute new matter absent evidence of support in the specification as originally filed. The new matter is noted to extend to Applicant's 371 priority document of PCT /US99/23134, 10-6-1999 and the

provisional 60/103,310, 10-6-1998 as filed. As set forth below, priority therefore cannot be established. As the instant specification is a mirror of the 371 filing Applicant's response should address how support for the claimed methods may be found within instant application as well as the provisional application of 60/103,310 if Applicant's are to obtain the benefit of the earliest priority date. Applicant's should particularly address all amendments to the claims as submitted 9-2-03 including all new limitations.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 4-8 and 11-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 recites "inducing aggregation of amyloidogenic proteins" but then requires measuring aggregation of alpha-synuclein. As aggregation of alpha-synuclein is not necessarily provided in the induction step, it is unclear how the artisan can then measure it in the same sample. Further, while applicant's intention may be that the "treatment" provides alpha-synuclein, such is not required of the claim. The discrepancy must be resolved such that the claim may actually be performed. Otherwise the claim is inoperable at least in part and would be subject to appropriate enablement rejections. The Examiner has not set forth such rejections at this time as it is deemed that the artisan is well versed in the scope of amyloidogenic proteins, their induction of aggregation and their requisite measure. Similarly the artisan is well versed

in the measurement of alpha-synuclein. Thus, while the particular claim elements appear to be enabled within the art, see also art rejections as set forth below, the method steps are indefinite in that the claimed method is not cohesive (the steps do not logically flow) and thus are incomprehensible in their requirements. The steps should not be implied but should be expressly recited.

Claim 4 repeats the recitation of "measuring aggregation of NACP/α-synuclein" and then recites the limitation "to test for a decrease in aggregaton, wherein the decrease is indicative of an effective treatment". The duplicate recitation is either an obvious error or reflective of a comparison not expressly recited. The claim apparently omits the relationship/comparison between the two measurements that is desired such that the "test for a decrease" is achieved. The test could be from the same sample from parallel samples or from different samples. The comparison that applicants intend should be recited as an element of the claim via steps and not simply implied.

Claims 5-6 recite "wherein oxidative stress is stimulated by a mixture of metal-ions and hydrogen peroxide" and "wherein oxidative stress is stimulated using an iron-catalyzed oxidative reaction". Yet, claim 4 does not apparently provide for "oxidative stress". Thus, the apparent steps of the claim appear to lack appropriate antecedent basis. If providing oxidative stress is intended to be either the "inducing" step or the "treatment" step as in claim 4, then claims 5 and 6 should appropriately reference such so that clear antecedent basis for the limitation is provided.

Further with respect to claims 5-8 and 11-13, it is noted that "oxidative stress" and "expression" are generally recognized in the art as cellular processes, yet the

claims do not denote that the induction, exposure or measurement steps are intracellular or involve exposure to any cell. As the steps appear to be stipulating exposure to a product, whereby the product is claimed via a "product-by process" recitation, the step is evaluated as a contacting with the product, regardless of the process by which it was made. If applicant's wish to recite the particular circumstances of the exposure, then the circumstances should be stated. For example, the claims should stipulate the presence of the agent/means required, i.e., nucleic acid and cell via which expression is achieved.

Priority

12. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Instant application claims priority from 60/103,310 filed 10-6-1998. Applicant's should note the new matter rejection of record. With respect to the priority document of 10-6-1999. Support for the claim recitations is similarly not found within the prior '310 provisional application. Accordingly the effective filing date awarded instant claims is

the date of 11-13-01 absent evidence for support in both instant application (371 of PCT/US99/23134, 10-6-1999 and the provisional 60/103,310, 10-6-1998 as filed.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

14. Claim 4 is rejected under 35 U.S.C. 102 (a) and (e) as being anticipated by Biere et al., US Patent 6,184,351 filed 9-24-1999 and issued 2-6-2001.

Biere et al., teach alpha-synuclein super mutants that accelerate alpha-synuclein aggregation thus, Biere teaches a method "comprising inducing aggregation of amyloidogenic (alpha-synuclein) proteins" as claimed. Biere et al., teach that Parkinson's disease (PD) is a neurodegenerative disorder which is pathologically characterized by the presence of intracytoplasmic Lewy bodies, the major component of which are filaments consisting of alpha-synuclein, see in particular abstract. Biere et al., teach an invention that provides alpha.-synuclein mutants which accelerate alpha-

synuclein aggregation and can thus be utilized for transgenic animal production and generation of the first progressive PD model. Biere et al., also provide an in vitro aggregation assay which can be utilized to identify alpha.-synuclein nucleation inhibitors for the treatment of PD. Thus, Biere teaches "A method for screening for treatments for neurodegenerative disease" as claimed. The method of Biere et al., includes exposure to a potential nucleation-affecting agent, see in particular claim 4 and thus Biere et al., teaches a method wherein the amyloidogenic proteins are induced to aggregate and then "expose(ed) to a treatment", wherein the comparison of the amount of aggregated α-synuclein is measured and assessed. As set forth in Biere et al., the assay is for alpha-nucleation inhibitors and such inhibitors are noted to be useful in the treatment of pathological conditions such as Parkinson's. The inhibitors are from a panel of drug candidates. Thus, Biere et al., teach "measuring aggregation of NACP/α-synuclein to test for a decrease in aggregation, wherein the decrease is indicative of an effective treatment."

15. Claims 4, 7-8 and 12-13 are rejected under 35 U.S.C. 102 (b) as being anticipated by Jensen et al., Biochem. J., 323:539-546, Apr. 15, 1997.

Jensen et al., teach that, "the identification of peptides that bind Abeta might open new possibilities for preventing the formation of AD plaques," the major pathology associated with Alzheimer's disease, see in particular pp. 545, column 2, lines 5-14. Jensen's "strategy is to identify small peptides that inhibit Abeta self-aggregation and the formation of complexes between Abeta and synucleins and their fragments....Future studies should show whether peptides derived from synucleins might prevent aggregations and whether they might be used as lead substances for the construction of drugs." Thus, Jensen et al., teach a screening based method for treatments of

Alzheimer's type neurodegenerative disease based upon the identification of molecules that inhibit aggregation of Abeta and synucleins. Jensen et al., teach methods for inducing aggregation of amyloidogenic proteins, see in particular Experimental, pp. 540, column 2, lines 24-44, and Results, Aβ binding to α- and β- synuclein, pp. 541-542, Figures 1-3. The amyloidogenic proteins were subject to treatment with BS3 crosslinker and the specificity of binding to alpha –synuclein was measured via SDS-PAGE analysis. Other treatments include incubation or exposure to Abeta, NAC, SDS, or β-synuclein. Thus, Jensen teaches "inducing aggregation of amyloidogenic proteins; exposing amyloidogenic proteins to a treatment; and measuring aggregation of α-synuclein". Jensen also teaches such measurements in the presence or absence of β-synuclein, Aβ and NAC. It was also shown that α-synuclein can form homodimers or heterodimers with β-synuclein, effectively teaching that β-synuclein can compete with α-synuclein for binding, see in particular Figure 4, and pp. 542, columns 1-2 paragraph spanning. Thus, Jensen teaches, "exposing amyoidogenic proteins to a tretment, measuring aggregation of α-synuclein to test for a decrease in aggregation wherein a decrease is indicative of an effective treatment." Further, Jensen notes that the complex formation is SDS sensitive. Thus, Jensen teaches that SDS, Aβ peptide, NAC and β-synuclein each compete or serve to inhibit α-synuclein aggregation and binding. Each of these results exhibit competition for α-synuclein aggregation/binding and thus are tests for decreases in aggregation as the molecules inhibit the formation of complexes. Moreover, the peptides are noted to aggregate and thus may be considered treatments as they are exposed to the amyloidoginic proteins as claimed. As claimed in claims 12-13 the method of Jensen includes treatment including exposure to the agent beta-synuclein and thus the reference encompasses the beta-synuclein

agent that promotes the expression of anti-amyloidogenic proteins. Thus the reference teachings anticipate the claimed invention.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 5-6 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hashimoto et al., NeuroReport 10:717-721, 1999 alone or alternatively in view of either Biere et al., US Patent 6,184,351 filed 9-24-1999 and issued 2-6-2001 or Jensen et al., Biochem. J., 323:539-546, Apr. 15, 1997.

Hashimoto et al., teach oxidative stress stimulated by iron and peroxide in the formation of amyloid-like aggregates of α-synuclein. Hashimoto et al., also taech that

such synuclein plaques are a major pathology in the brains of patients with Parkinson's and Lewy Body disease. Hashimoto et al., further teach that the iron chelator deferoxamine was able to inhibit the iron-catalyzed oxidative reaction that stimulated aggregation, see in particular abstract, Results, pp 718-20 and Figures 1-2. Thus, Hashimoto et al., teach a method including "inducing aggregation of amyloidogenic proteins, exposing amyloidogenic proteins to a treatment and measuring aggregation of NACP/alpha-synuclein and testing for a decrease in aggregation. The treatment of deferoxamine is noted to be a treatment that decreases aggregation.

Hashimoto et al., fall short of suggesting that such assays could be used for the purpose of screening for treatments for neurodegenerative disease and that such decreases in aggregation would be indicative of effective treatments for neurodegenerative disease. Such are the claim recitations within the preamble and outcome of the claimed method.

However, one of skill in the art would have been motivated to use the assay of Hashimoto et al., in a screen for molecules capable of inhibiting alpha-synuclein aggregation for potential use as therapeutics to treat Parkinson's and Lewy body disease as the skilled artisan recognizes that the assay was effective and beneficial in finding a compound that was capable of inhibiting alpha-synuclein aggregation in vitro. The artisan is well apprised of the need for treatments which both inhibit oxidative stress in the brains of Parkinsons and Lewy body patients and the need for drugs to inhibit alpha-synuclein plaque formation because as Hashimoto evidences, alpha-synuclein plaques are recognized as the major pathology in such patient's brains. In particular,

Hashimoto et al., teach within the discussion that "since iron promotes NACP/α-synuclein self-aggregation, it is possible that aberrant accuulation of ferric ion might act a s a risk factor for the aggregation ...in the PD brain. Indeed, it has been suspected that the shift from ferrous to ferric ion may be a risk factor in PD. Riederer et al., showed that the ratio of ferric to ferrous ion in the substantia nigra of patients with advanced PD was remarkably increased compared with controls." In conclusion Hashimoto summarizes other data saying, "it is reasonable to speculate that aggregation of NACP/α-synuclein is not only a result of increased ferric ions via oxidative reaction but can also be a trigger/stimulator of the iron-catalyzed oxidative reaction....The present study suggests that reactions involving oxidative stress might lead to aggregation of NACP/α-synuclein...It is then possible that this abnormally aggregated molecule might mediate the neurodegenerative process through mechanisms that remain unclear." Thus, the artisan is apprised of the links of oxidative stress in the formation of pathological alpha-synuclein aggregates in PD and Lewy body brains and would expect that inhibition of this mechanism would be effective in ameliorating alpha-synuclein plaque formation. Accordingly one of skill would be motivated to assess the a molecule resulting in the inhibition of alph-synuclein aggregation as one of therapeutic benefit it Parkinson's and/or Lewy body disease. One of skill in the art would have further expected success in identifiying potential treatments using such screening assays given the positive results of Hashiimoto in identifying molecules that inhibit alpha-synuclein aggregate formation give that Hashimoto teaches that such is the pathological basis of the plaque formations in

patients with Parkinson's and Lewy body disease.

Should Hashimoto et al., with the discussion and relative skill in the art alone not be enough to convince applicants of the obviousness of the preamble recitation and indication of effective treatments with decreases in alpha-synuclein aggregation, further motivation is provided to the artisan for such screening assays via Biere and Jensen. These references as set forth above teach the use of the disclosed assay to screen for treatments for neurodegenerative disease and that agents that act as inhibitors or result in decreases of aggregation are the compounds deemed to be appropriate for such treatments. Biere and Jensen each teach the same assay methods wherein the goal is to identify potential candidate treatments and/or therapeutics via assay for decreases or inhibition of α-synuclein amyloidogenic aggregation. Thus, Biere and Jensen provide the motivation to use the method of Hashimoto as a screening assay in which suitable inhibitors may be found as exemplified in the Hashimoto reference. Hashimoto teaches that an iron-catalyzed oxidative reaction induced via a mixture of ferric ion and peroxide is effective to increase aggregation of α-synuclein. Hashimoto et al., also teach defrroxamine inhibition of alpha-synuclein aggregate formation. Thus, in light of the methods of Biere and Jensen the artisan would have been motivated to use the alternative procedures of inducing aggregation using ferric ion and peroxide as demonstrated by Hashimoto or treatment with deferroxamine to inhibit alpha-synuclein aggregation. One of skill in the art would have expected success using such modification based upon the teachings of Hashimoto et al., that such treatment is effective to induce and/or inhibit α-synuclein aggregation. The cumulative references

teach the required motivation and expectation of success for the screening method as claimed and thus the invention is obvious to the artisan in light of the reference teachings.

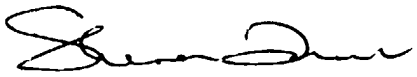
Status of Claims

18. No claims are allowed.

19. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (703) 308-0056. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 6:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached at (703) 308-4623.



Sharon L. Turner, Ph.D.
November 3, 2003